OPEN

CASE REPORT

Heparin Insensitivity and Thrombotic Risk Associated With Sequential Uses of Prothrombin Complex Concentrate and Andexanet Alfa for Apixaban Reversal During Acute Type A Aortic Dissection Repair: A Case Report

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The management of patients on direct oral anticoagulants (DOACs) who require emergent cardiac surgery is slowly evolving. The introduction of andexanet alfa, a novel antidote for apixaban and rivaroxaban, added a specific reversal agent to our armamentarium, but its safety and efficacy are still being investigated. We report 2 patients on DOAC treatment who required emergency cardiac surgery. Both received perioperative andexanet alfa together with prothrombin complex concentrate (PCC) at some time during 6 hours before operative management. Heparin resistance was noted in each instance, and pump thrombosis developed in 1 case. (A&A Practice. 2022;16:e01636.)

GLOSSARY

4F-PCC = 4 factor prothrombin-complex concentrate; **ACT** = activated clotting time; **AT** = antithrombin; **CPB** = cardiopulmonary bypass; **DHCA** = deep hypothermic circulatory arrest; **DOACs** = direct oral anticoagulants; **EQUATOR-CARE** = Enhancing the Quality and Transparency of Health Research-Consensus Based Clinical Case Reporting; **FDA** = Food and Drug Administration; **FFP** = fresh frozen plasma; **FIBTEM** = fibrin-based thromboelastometry; **FIX** = factor IX; **FX** = factor X; **FXa** = factor Xa; **HEPTEM** = heparinase-based thromboelastometry; **HIPAA** = Health Insurance Portability and Accountability Act; **ICU** = intensive care unit; **II** = prothrombin; **IIa** = thrombin; **IUs** = international units; **IV** = factor IV; **OR** = operating room; **PCC** = prothrombin-complex concentrate; **RCP** = retrograde cerebral perfusion; **TFPI** = tissue factor pathway inhibitor; **U** = units; **Va** = activated factor V; **Xa** = activated factor X

Andexanet alfa, approved in 2018 for emergent reversal of rivaroxaban or apixaban, is a recombinant modified human factor Xa (FXa) decoy molecule that serves as an alternative target for the aforementioned direct oral anticoagulants (DOACs). It is a catalytically inactive protein and, therefore, cannot directly activate prothrombin or inhibit the prothrombinase complex.[1] Procoagulant actions of andexanet alfa involve several mechanisms. It reduces the inhibition of native Xa and restores its ability to convert prothrombin to thrombin. It enhances tissue factor-triggered thrombin generation by inhibiting tissue factor pathway inhibitor (TFPI).[2]

Given its affinity for antithrombin (AT), in patients requiring urgent cardiopulmonary bypass (CPB), there are anecdotal data suggesting it may precipitate heparin insensitivity and CPB circuit thrombosis in vivo.[3–6] Flaherty et al[5] reported severe heparin resistance following 2 doses of andexanet alfa for reversal of apixaban in the setting of emergent cardiac surgery. A very high dose of heparin (~80,000 units [U]) was required to achieve therapeutic activated clotting time (ACT), but no evidence of CPB circuit thrombosis was seen. Erdoes et al[6] also noted heparin resistance and CPB circuit thrombosis following andexanet alfa administration in an emergent cardiac surgery for cardiac tamponade. The sequential use of PCC and andexanet alfa in our cases, albeit considered imprudent in hindsight, has not been previously explored and provides insights into andexanet alfa-associated heparin resistance and the possibility of thrombotic "synergy" when both drugs are utilized. It is important to note that the time between PCC and andexanet alfa administration in the first case was

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approximately 3 hours as the PCC was given at an outside hospital immediately before transfer to our facility. Finally, little is known about the safety and efficacy of how andexanet alfa interacts with other commonly administered anticoagulant reversal agents, such as PCC and protamine. This report details 2 cases from 2 institutions that both describe the perioperative use of PCC together with andexanet alfa for apixaban reversal in the setting of an emergent type A aortic dissection with subsequent heparin resistance and 1 case of CPB circuit thrombosis.

IRB approval was not sought as the number of patient cases is <4. A written Health Insurance Portability and Accountability Act (HIPAA) authorization to use and disclose existing protected health information was obtained from the subjects of this case report. This article adheres to the applicable EQUATOR-CARE guideline.

CASE REPORT(S)

Case 1

The first case is a 67-year-old, 80-kg man who underwent emergent surgical repair for a type A aortic dissection with acute tamponade physiology. His medical history included atrial fibrillation on apixaban and heart failure with severely reduced ejection fraction. He was diagnosed with a Type A dissection at an outside hospital and administered 3779 international units (IUs) of 4 factor PCC (4F-PCC) for apixaban reversal at 12:41 PM at the outside facility. On arrival at our hospital approximately 5 hours after symptom onset, he was brought directly to the OR due to concern for acute tamponade. After induction, an emergent pericardial window was performed with evacuation of 1.5 L of blood. Subsequent to central line placement, an initial dose of 23,000 units (U) of IV heparin was administered at 2:52 PM; this resulted in an ACT of 865 s (baseline was 213 s and threshold for safe institution of CPB at this institution is an ACT >300, with a goal ACT >480 for the duration of the case while centrally cannulated on CPB). Given his high risk for bleeding and unclear timing of his last apixaban dose, he was then treated with a full dose of andexanet alfa (800 mg over 30 minutes followed by an infusion of 8 mg/min over 120 minutes) at 3:30 PM.

While under deep hypothermic circulatory arrest (DHCA), which started at 3:50 PM, retrograde cerebral perfusion (RCP) was initiated while beginning an aortic root and hemiarch repair up to the patients prior thoracic aortic graft near the take off of the left subclavian artery. He developed presumed heparin resistance with low ACT values of 145 and 150 seconds shortly after 4:00 PM despite additional heparin doses of 10,000 and 15,000 U. It was at this time that the perfusionist noted clot developing in the venous CPB reservoir, at which time RCP was stopped. Prompt exchange of the entire pump volume and circuit was performed with packed red blood cells and fresh frozen plasma (FFP) for a prime. The andexanet alfa infusion was discontinued at this time, and CPB resumed at 4:24 PM. 500 IU of AT (Thrombate III; Grifols) were administered, with appropriate ACTs for the duration of bypass. Following the emergent exchange of the entire volume of the CPB circuit, a significant coagulopathy developed with a platelet count of $7 \times 10^3/\mu L$ and flat-line tracings on heparin-neutralized HEPTEM and FIBTEM thromboelastometry tests (Instrumentation Laboratory). After extensive blood product transfusion and resuscitation, he was successfully weaned off CPB and was admitted to the intensive care unit (ICU) on moderate inotropic and pressor support. On postoperative day 3, he was extubated, alert, oriented, conversational, and neurologically intact.

Case 2

The second case involves a 76-year-old, 67-kg woman who presented with sudden onset, severe chest pain radiating to her back. Her medical history included atrial flutter on low-dose apixaban (2.5 mg daily), coronary artery disease, previous cerebrovascular accident (one and a half years prior), and a remote history of unprovoked pulmonary embolism. Initial laboratories showed an antifactor Xa level of 1.6 IU/mL (therapeutic range for apixaban is 1.8–2.2 IU/mL). A computed tomography angiogram revealed a type A aortic dissection. She was given 2193 IU of 4F-PCC at 6:30 PM and taken emergently to the operating room for aortic repair.

After induction, a 400 mg bolus of andexanet alfa was initiated at 7:11 PM and given over 30 minutes. A low-dose infusion was then started (4 mg/min). Following sternotomy, she received a 400 U/kg bolus of heparin (27,000 U, 7:48 PM) with an initial ACT of 155 seconds. Several additional boluses of heparin totaling 52,000 U were administered with a peak ACT of 221 seconds. Four units of FFP were given, and the andexanet alfa infusion was ultimately discontinued (8:45 PM, total infusion dose administered 264 mg) due to concern for heparin resistance. The resultant ACT was 331 seconds, and CPB was successfully initiated at 8:50 PM. Throughout the bypass run, ACT times remained persistently low in the 200–300's range despite administration of 6 additional units of FFP. Despite these ACT times and administration of apixaban reversal, no thrombosis was noted throughout the case. Ultimately, the surgeon successfully performed a Hemashield graft placement to the ascending aorta and hemiarch, with a descending aortic elephant trunk graft. DHCA was utilized during the case. The patient was given protamine, and uneventfully weaned off bypass. She required 1 postoperative 50 mg dose of protamine overnight.

She was extubated on postoperative day 3. Her postoperative course was complicated by encephalopathy and acute-on-chronic respiratory failure requiring persistent noninvasive positive pressure ventilation and significant supplemental oxygen support. On postoperative day 11, a family discussion was held regarding the patient's prognosis. Her family did not believe the patient would have wanted to pursue a tracheostomy, and given her postoperative neurological failure, they requested she be transitioned to comfort care. The patient died that evening.

DISCUSSION

Patients on DOACs undergoing emergent cardiac surgery risk uncontrolled hemorrhage during and after CPB may require immediate reversal of their anticoagulated state in an attempt to prevent the high morbidity and mortality associated with uncontrolled intraoperative and postoperative bleeding. There is currently a paucity of data on andexanet alfa, PCC, and their combination in perioperative reversal of anti-Xa agents, particularly in patients undergoing systemic

heparinization for CPB. Additionally, there are limited data on the use of these agents during low-flow states, such as the low flow that occurs during DHCA. While PCC is not currently FDA approved for the reversal of DOACs and is, therefore, considered "off-label," its use in this regard is commonplace and is referenced by the 2018 European Heart Rhythm association guidelines in relation to reversal of DOACs in the setting of life-threatening bleeding.[7]

Heparin anticoagulation is dependent on AT, and heparin induces conformational changes in the AT molecule that facilitate binding of AT-heparin complex to thrombin and FXa. While andexanet alfa acts as a decoy Xa molecule, binding circulating anti-Xa drug, it also binds to AT-heparin and competes with endogenous FXa for AT binding.[8]

Andexanet alfa thus sequesters large amounts of heparin-bound AT molecules as well as apixaban,[1] allowing endogenous FXa and thrombin to promote heparin resistance and clotting (Figure 1). In addition to promoting AT depletion, andexanet alfa also binds TFPI.[2] TFPI is a potent regulator (inhibitor) of early FXa activation; therefore, relative TFPI deficiency due to andexanet alfa binding promotes FXa generation and coagulation. Large amounts of additional heparin, AT concentrate, and/or plasma transfusion were required to overcome heparin resistance in both these cases. Each 500 IU of AT concentrate and 1 U of FFP only increase AT activity by 10% and 3%, respectively. A higher dose of AT (2500–3000 IU) might have expedited the recovery of AT activity. In both cases, therapeutic doses of PCC were administered (47.2 and 33.8 IU/kg), and thus, supranormal prothrombin, FIX, and FX levels would be expected in these patients. Elevated prothrombin is known to enhance thrombin generation in vitro, and low AT state following the infusion of andexanet alfa is presumed to synergistically increase thrombogenicity of PCC.[9] Additionally, CPB reservoirs are known to create blood stasis, which predisposes them to thrombus formation as reported in the cases utilizing direct thrombin inhibitors.[10–11] Low-flow states such as those that occur during the DHCA used in aortic surgery can exacerbate the risk of thrombosis.

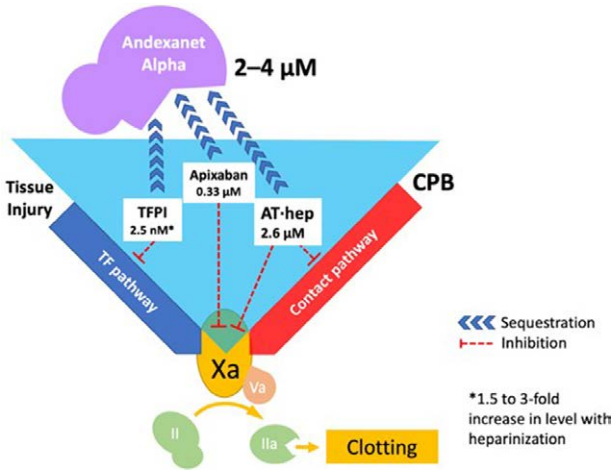

Figure 1. Schemata of the interactions of andexanet alfa with apixaban, tissue factor pathway inhibitor, and heparin-bound AT plasma concentrations of andexanet alfa are approximated to be at 2–4 μM after 400–800 mg bolus injection, which is close to plasma level of AT. Heparin administration induces a conformational change in AT to sequestration of heparin-bound AT (AT·hep) to andexanet alfa. Apixaban and TFPI are sequestered to andexanet alfa as well, and their plasma levels are relatively low compared to AT. The lack of heparin-bound AT mediated inhibitions of contact activation causes heparin insensitivity and possibly thrombus formation. AT indicates antithrombin; CPB, cardiopulmonary bypass; IIa, thrombin; II, prothrombin; Va, activated factor V; Xa, activated factor X; TFPI, tissue factor pathway inhibitor.

In summary, we observed severe heparin resistance in 2 cases after concomitant uses of PCC and andexanet alfa and 1 case of CPB circuit thrombosis in the presence of systemic heparinization. Although andexanet alfa is considered a decoy, it retains abilities to interact with multiple endogenous anticoagulant proteins. It is critical for perioperative clinicians to understand dynamic coagulation changes, which can easily shift from anticoagulant to procoagulant state as demonstrated here by the coadministration of andexanet alfa, heparin, and PCC. These cases add to the body of literature again demonstrating severe heparin resistance with andexanet alfa, and further validate the concerns raised by Levy and Welsby in their editorial to the Flaherty paper emphatically stating that andexanet use should be avoided in cardiac surgery requiring bypass due to the severe risks already noted.[12] We additionally illustrate the prothrombotic state that exists with coadministration of andexanet alfa and PCC during the CPB period not previously described.

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